REMARKS

This amendment is responsive to the Office Action mailed May 16, 2003. Original Claims 1-11 are under examination in the present action. Claims 1-5, 7, 8, 10 and 11 stand rejected. Claims 6 and 9 are objected to for being dependent on a rejected base claim.

The Examiner has objected to the Abstract of the disclosure because of the excessive length and because of the inclusion of legal phraseology, e.g., the recitation "said". Additionally, the Examiner contends the Abstract is insufficient as to the details of the particular pharmaceutical uses of the claimed compounds. Applicants submit herein a new replacement Abstract conforming to the requirements of MPEP §608.01(b). Withdrawal of the objection to the Abstract is believed to be in order.

Additionally, the Examiner notes that the requirements for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e) have not been met, i.e., the specification does not contain a reference to the prior-filed provisional application. Applicants have amended the specification herein to contain a statement cross-referencing the related applications and claiming priority to Applicants' provisional application under 35 U.S.C. §119(e). This application is a nonprovisional application that entered the national stage after compliance with 35 U.S.C. §371 from an international application filed under 35 U.S.C. 363 before November 29, 2000. Therefore, in accordance with 37 C.F.R. §1.78(a)(5)(ii)(B), no fee or petition is believed to be due for amending the specification to perfect priority.

The Examiner also objects to the specification and requests that Applicants update the status of referenced U.S. patent applications. Applicants have herein amended the specification to update the status of the U.S. applications where appropriate.

Withdrawal of the objection to the specification is believed to be in order.

Claims 8 and 11 have been amended herein to more particularly point out and distinctly claim that which Applicants regard as their invention. Support for the claim amendments is apparent from the original claims. No new matter is added.

Response to issues presented under 35 U.S.C. §112, second paragraph

Claims 8 and 11 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, the Examiner contends that Claim 8 is incomplete because it does not set forth formula (I) in the body of the claim. Applicants have amended Claim 8 herein to depend from Claim 1, as suggested by the Examiner, which is believed to obviate these rejections.

Similarly, Claim 11 stands rejected because there is no antecedent basis in the claims for the recitation "said human or other animal". Applicants have amended Claim 11 herein to delete the recitation and to specify that cells are treated *in vitro*.

The claims, as amended, are definite. Accordingly, withdrawal of the rejection of Claims 8 and 11 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Response to issues presented under 35 U.S.C. §103

Claims 1-5, 7, 8, 10 and 11 stand rejected under 35 U.S.C. §103(a) as being unpatentable over international application number PCT/US97/22251 (publication number WO 98/24807). Specifically, the Examiner contends the reference teaches

compounds of the formula set forth in Claim 1 wherein residue A^6 can be Abu, beta-Ala, Gaba, or Val. The Examiner concludes:

> "Applicants have stated in their specification that their claimed compounds have unexpected agonist as opposed to antagonist activities...However, in the absence of a probative comparison of the closest prior art compounds of the WO Patent Application '807 and of Applicants' claimed compounds in the same assay, Applicants' statement in and of itself can not be relied upon to rebut the prima facie case of obviousness set forth above." (Office Action, paper no. 7, page 5.)

As taught in the specification on page 2, lines 14-16, the peptides of the present invention are a previously undefined sub-genus encompassed by the genus of compounds disclosed and claimed in WO 98/24807. Similar to the compounds of the WO 98/24807 application, the compounds of the present invention, i.e., compounds of formula (I) (Claim 1), possess high affinity for somatostatin receptors. In contradistinction to the compounds of the WO 98/24807 application, however, the compounds of the present invention were surprisingly discovered to possess agonist activity.

The courts have made it clear that unexpected scientific data that demonstrates an improvement over the disclosure of the closest prior art is an important indicator of non-obviousness, i.e., it is sufficient to overcome even a *prima facie* case of obviousness. For example, in *In re Soni*, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995), the applicant, Soni, claimed a composition comprising an organic polymer with a molecular weight greater than 150,000 and a particulate conductive filler. Additionally, the applicant claimed that the composition demonstrated unexpected and significant improvements over the properties of compositions of the prior art, which utilized organic polymers with molecular weights less than 150,000. Soni also included

test data comparing the properties of the claimed invention, i.e., organic polymers with molecular weight greater than 150,000, with those of the prior art, i.e., organic polymers with a molecular weight less than 150,000. The examiner and the PTO Board of Appeals dismissed the applicant's data, essentially stating that one skilled in the art would expect higher molecular weight polymers to result in better composition properties and further stating that the unexpected results consisted of conclusory statements unsupported by any factual data.

Soni appealed to the Federal Circuit, where the issue was whether the data in Soni's patent specification showed that the claimed compositions demonstrated "unexpectedly improved" properties compared to the prior art lower molecular weight compositions. According to the Court,

> "One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results", i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." 54 F.3d at 750, 34 USPQ2d at 1687 (emphasis added).

Additionally the Court stated,

> "The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or a process may yield substantially different results." 54 F.3d at 750, 34 USPQ2d at 1687 (emphasis added).

After analyzing the data in Soni's application, the Court overturned the Board's holding, stating, "In our view, however, when an applicant demonstrates *substantially* improved results, as Soni did here, and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of*

evidence to the contrary." 54 F.3d at 751, 34 USPQ2d at 1688. (emphasis in original).

In the present case, the Examiner contends that absent data comparing the antagonist compounds to the presently claimed agonist compounds, the peptide modifications of the present application are obvious over the previously disclosed genus of antagonist peptides. In response, Applicants note that the following experiments were conducted to determine the *antagonistic* properties of the genus compounds (*See*, WO98/24807, pages 29-32):

Bioassay on the *In vitro* Release of Growth Hormone

(a) Rat Pituitary Cell Dispersion

> Pituitaries from adult Charles River CD male rats (Wilmington, MA) housed under controlled conditions were dispersed and cultured using aseptic technique. Pituitaries were removed from sacrificed rats, sectioned, and then placed into a siliconized, liquid scintillation vial containing 2 ml 0.2% trypsin (Worthington Biochemicals, Freehold, NJ) in sterile-filtered Krebs-Ringer bicarbonate buffer supplemented with 1% bovine serum albumin, 14 mM glucose, modified Eagle medium (MEM) vitamin solution, and MEM amino acids (Gibco Laboratories, Grand Island, NY) (KRBGA). All glassware was siliconized as described by Sayers, et al., Endocrinology 88:1063 (1971). The fragments were incubated in a water bath for 35 minutes at 37°C with agitation. The vial contents then were poured into a scintillation vial containing 2 ml 0.1% DNase (Sigma Chemical Co., St. Louis, MO) in KRBGA and incubated for 2 min at 37°C with agitation. After incubation, the tissue was decanted into a 15 ml centrifuge tube and allowed to settle. Medium was discarded, and pituitary sections were washed 3 times with 1ml fresh KRBGA. The cells were then dispersed in a 2 ml 0.05%

LBI (lima bean trypsin inhibitor, Worthington Biochemicals) by gently drawing the fragments into and expelling them out of a siliconized, fire-polished Pasteur pipette. Dispersed cells were then filtered through a 630 μm diameter Nylon mesh (Tetko, Elmsford, NY) into a fresh 15 ml centrifuge tube. An additional 2 ml of 0.05% LBI solution was used to rinse the first tube and was transferred to the second tube with filtering.

(b) Cell Culture

The dispersed cells were then further diluted with approximately 15 ml sterile-filtered Dulbeccol's modified Eagle medium (GIBCO), 3% horse serum (GIBCO), 10% fresh rat serum (stored on ice for no longer than 1 hr) from the pituitary donors, 1% MEM non-essential amino acids (GIBCO), and gentamycin (10 ng/ml; Sigma) and nystatin (10, 000 U/ml; GIBCO). The cells were poured into a 50 ml round-bottomed glass extraction flask with a large diameter opening and then randomly plated at a density of approximately 200,000 cells per well (Co-star cluster 24; Rochester Scientific Co., Rochester, NY). The plated cells were maintained in the above Dulbeccols medium in a humidified atmosphere of 95% air and 5% CO_2 at 37°C for 4-5 days.

(c) Experimental incubation and IC_{50} determination

In preparation for a hormone challenge, the cells were washed 3 times with medium 199 (GIBCO) to remove old medium and floating cells. Each treatment well contained a total volume of 1 ml medium 199 containing 1 % BSA (fraction V; Sigma) with treatments as described below. Each antagonist candidate was tested using a single 24-well cell culture plate. Each treatment was performed in triplicate. Each plate contained 8 treatment groups: one 1 nM growth hormone releasing factor (GRF) (1-29)NH_2-stimulated control group; one 1 nM somatostatin-inhibited control group in the presence of 1 nM GRF(1-29)NH_2; and 6 doses of a given antagonist in the presence of both 1nM SRIF

(Somatostatin) and 1 nM GRF per plate. After 3 hrs at 37°C in a air/carbon dioxide atmosphere (95/5%), the medium was removed and stored at - 20°C until radioimmunoassayed for growth hormone content. IC_{50}'s of each antagonist versus 1 nm @ SRIF were calculated using were calculated using a computer program (SigmaPlot, Jandel Scientific, San Rafael, CA) with the maximum response constrained to the value of the 1 nm GRF(1-29)NH_2-stimulated control. The IC_{50} values, the analog concentration wherein 50% inhibition of the response is achieved, are listed below:

Analog No.	Compound	IC_{50} (μM)
1	[formula not found]	3.03
2	H_2-β-Nal-DCys-Tyr-DTrp-Lys-Val-Cys-β-Nal-NH_2	0.04
3	H_2-β-Nal-DCys-Pal-DTrp-Lys-Val-Cys-β-Nal-NH_2	0.01
4	H_2-Phe-DCys-Pal-DTrp-Lys-Val-Cys-β-Nal-NH_2	0.03
5	(CH_3CO)-β-Nal-DCys-Tyr-DTrp-Lys-Val-Cys-β-Nal-NH_2	0.06
6	H_2-Phe-DCys-Pal-DTrp-Lys-Thr-Cys-Thr-NH_2	0.9
7	H_2-D-p-Cl-Phe-DCys-Pal-DTrp-Lys-Tle-Cys-p-Cl-Phe-NH_2	0.071
8	H_2-D-β-Nal-DCpa-Tyr-DTrp-Lys-Val-Phe-Thr-NH_2	3.96
9	H_2-D-β-Nal-DCys-Tyr-DTrp-Lys-Val-Cys-β-Nal-NH_2	1.36
10 *	H_2-Dip-DCys-Pal-DTrp-Lys-Val-Cys-Dip-NH_2	0.62

*See WO 98/24807, page 32, for complete listing of IC_{50}'s for all 57 analogs tested.

In order to show unexpected results over the above-reference, the Examiner requests that Applicants provide data comparing the agonist compounds of the present invention to the antagonist compounds of the reference in the same assay. However, Applicants submit that a side-by-side comparison would not be probative in this case, as an antagonist by definition would not have agonist activity, and conversely, an agonist would not have antagonist activity with respect to the receptor binding. Rather, Applicants submit herewith the affidavit of Dr. John E. Taylor, pursuant to Rule 132, introducing experimental data illustrating the surprising agonist activity of the compounds of the present invention. In particular, the affidavit includes specific somatostatin receptor affinity data and somatostatin receptor activation (agonist) data for the two exemplary compound embodiments described in the application, namely:

Cpa–cyclo(DCys–3–Pal–DTrp–Lys–Ala–Cys)–Nal–NH_2 (Example 1 in the specification), and

Cpa–cyclo(DCys–3–Pal–DTrp–Lys–Gaba–Cys)–Nal–NH_2 (Example 2 in the specification).

Applicants submit that the data provided herein show the relative specificity of the present compounds for human somatostatin receptors, in particular somatostatin receptor 5, as well as their ability to evoke a somatostatin-like response from cells expressing a somatostatin receptor, i.e., somatostatin agonist activity. These results are particularly unexpected, considering the compounds of the cited publication WO 98/24807 were taught to possess antagonistic properties for somatostatin receptors. Applicants' discovery and definition of an unexpected group of agonist compounds within a class of antagonist compounds clearly indicates, as in In re Soni, nonobvious subject matter.

Therefore, since the compounds of the present invention possess advantageous and unexpected properties that could not have been perceived or imagined by those skilled in the art from consideration of WO 98/24807, Applicants request reconsideration and withdrawal of the rejection of Claims 1-5, 7, 8, 10 and 11 under 35 U.S.C. §103(a).

Applicant respectfully submits that the claims are in a condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to telephone Applicant(s) attorney at (508) 478-0144 to facilitate prosecution of this application.

Please apply any charges or credits to Deposit Account No. 50-0590 referencing attorney docket number 00537-191002.

Respectfully submitted,

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